REMARKS

Claims 1-56 are currently pending. Claims 1,3, 13, 15, 25, 27, 41 and 43 have now been amended. Claims 2, 14, 26, and 42 have been canceled. Applicants respectfully assert that all amendments are supported by the original disclosure and do not introduce new matter. The specification has also been amended to comply with the Examiner's request.

Applicants appreciate Examiner's reconsideration and withdrawal of the election of the species indicated as 1) administering a DNA and 2) administering an mRNA.

By way of review, the present invention relates to a targeted treatment for cancer with low systemic toxicity. The invention relies on the fact that tumor cells display elevated levels of the translation initiation factor, eIF4E. The eIF4E protein has been shown to be rate-limiting in cells for the initiation of protein synthesis. The eIF4E protein binds to the 5'm7pppG cap structure common to polyadenylated mRNAs and is part of a larger translation initiation complex (eIF4F) that is thought to bind to the 5' cap, unwind secondary structure in the 5' untranslated region (5' UTR) of mRNAs, and facilitate identification of the AUG initiation codon and 40S ribosomal recruitment and positioning. Messenger RNAs that contain sequences of long G/C rich 5'UTRs are poorly translated, including the vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) mRNAs. In cells overexpressing eIF4E, VEGF and FGF2 mRNAs are efficiently translated.

The present invention provides for a method of treating cancer using a chimeric DNA construct where, a toxin gene (for example, the herpes simplex virus type-1 thymidine kinase gene (HTK)) is immediately downstream of a 5' UTR sequence having a complex secondary structure. The HTK gene is a widely used "suicide" gene, which can convert the prodrug ganciclovir (GCV) to a toxic metabolite in HTK expressing cells. The GCV metabolite acts as a chain terminator during DNA replication and consequently leads to HTK-expression and cell death.

The use of suicide genes in combination with pro-drugs is well known in the art and clinical trials assessing the efficacy of this approach have been successfully carried out.

The unique aspect of applicant's invention is that a toxin gene can be efficiently translated only in eIF4E overexpressing cells, and is poorly translated in normal surrounding cells. As such, this novel approach confers *tumor specific expression* of the toxin gene in the absence of a tissue or tumor-specific targeting sequence and results in specific killing of tumor cells without undue collateral damage to normal cells in the body. The treatment may be used for both a primary tumor as well as secondary metastases.

Thus, unlike traditional gene therapy techniques, this technology allows one to specifically affect tumor cells—without relying upon any targeting of the construct to specific cells—while leaving normal cells relatively unscathed. Previously, tumor restricted expression of a suicide gene such as HTK has relied on either localized administration of the delivery vector (typically via intratumor injection) or a tissue or tumor specific promotor. These techniques usually require specific knowledge of the cancer type and must be tailored almost individually. The present invention, in contrast, is applicable to most solid tumors. This represents a significant advance for suicide gene therapy of solid tumors.

Priority

Applicants have now amended the first paragraph of the specification such that the status of the prior application as now issued is included in the priority information in the first line of the specification.

Claim Objections

The Office has objected to claims 2, 14, 26, 42 because the claims recite the phrase "folded state free energy AG <about -50Kcal/Mol." The phrase should be "folded state free energy $\Delta G \leq$ about -50Kcal/Mol." This is a typographical error due to the font and the appropriate claims have now been amended to recite as "folded state free energy ΔG about $\leq$ -50 Kcal/Mol."

Claim Rejections - 35 USC § 112, Second Paragraph

The Office has rejected claims 26-40 under 35 U.S.C. § 112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 previously recited the phrase, "The method as recited in claim 2$" in line 1, making it unclear as to which of the other claims claim 26 depends. The Office further rejected Claims 27-40 due to the dependency of these claims on claim 26. Claim 26 has been canceled, the language of that claim incorporated into dependent claim 25. The dependency of all remaining claims should now have proper dependency, rendering the rejection under 35 USC § 112, Second Paragraph, moot.

Claim Rejections - 35 USC § 112, First Paragraph

a. Written Description

The Office has rejected claims 1, 13, 16-24 and 41 under 35 U.S.C. § 112, First Paragraph, as failing to comply with the written description requirement, asserting that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that applicants were in possession of the claimed invention at the time of filing.

The Office bases this rejection on the "large genus" encompassed by the claims. The Office argues that applicants "have only disclosed a vague description of a structure characteristic of a genus comprising potentially millions of different possibilities..." To support this rejection, the Office cites *Fiers v. Sugano* and *Vas-Cath Inc. v. Mahurkar*. Applicants respectfully disagree with this analysis. It is Applicants' position that the present specification more than adequately discloses and corresponds to the presently claimed subject matter.

As an initial matter, the claims are presently amended to add the feature of a sequence having a stability measured as folded state free energy of $\Delta G \leq$ about -50 Kcal/Mol. As such, the number of claimed sequences is vastly reduced, and that one of ordinary skill in the art may readily determine a species encompassed by this genus. This amendment further characterizes

the properties of the 5'UTR such that a much smaller, and determinable, group of sequences can readily be determined by one of ordinary skill in the art. Should the Office require applicants to limit the claims to a specific sequence, applicants would effectively be deprived of their invention due to the redundancy of the genetic code and the ability of one of skill in the art to readily mutate a specific sequence while still arriving at the essential features of applicant's invention.

With respect to the Office's rejections under 35 USC § 112, First Paragraph, the Office is reminded of the goals of the written description requirement. These are 1) to clearly convey the information that an applicant has invented and the subject matter which is claimed and 2) to put the public in possession of what the applicant claims as the invention. *MPEP §2163*. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). The written description guidelines regarding genus/species situations require only a satisfactory disclosure of a "representative number' of the species to show that the applicants had possession of the genus in view of the species disclosed. As noted by the Office, satisfactory disclosure "depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Office Action, p.5, citing Revised Guidelines for the Written Description Requirement*. The Office is reminded that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *MPEP § 2163*.

Applicants respectfully assert that these requirements have been met, and that the disclosure adequately provides a written description such that one of ordinary skill in the art (which is deemed to be quite high) would be reasonably led to a particular species suitable for carrying out the claimed invention.

In fact, while the specification of the present application does not contain DNA sequence listings for nucleic acid sequences that have the ability to inhibit translation in the absence of eIF4E and allow translation in the presence of eIR4E, the specification does provide for

examples describing the use of 5' UTRs from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase. The sequences of such specific examples are very well-known in the art. Further, the disclosure of untranslated sequences having "a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G \leq$ about -50 Kcal/Mol" further provides meaningful, specific guidance that would allow one of ordinary skill in the art to "immediately envisage" the claimed invention.

The 5' UTRs described offer a representative number of members of the genus showing the attributes or features as necessary for those skilled in the art. The Office has relied on *Fiers v. Sugano* to reject the present claims. *Fiers* relates to an interference proceeding in which the court found that the *Fiers* application did not meet the written description requirement with regard to the following count: "a DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." *Fiers* at 1603. No such DNA sequence was disclosed in the *Fiers* application. The court held that the specification did not meet the written description requirement as conception of the claimed DNA did not occur upon conception of a method for obtaining it, but rather upon the inventor envisioning the detailed chemical structure of a gene so as to distinguish it from other materials and a method for obtaining the gene. In contrast to the count at issue in *Fiers*, the present application discloses and relies upon DNA sequences fully known in the art that are useful in the practice of the claimed invention, *i.e.*, the 5' UTRs from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase, and characterized by a specific folded state free energy that is not inherent to all mRNA sequences. Thus, Applicants respectfully submit that *Fiers* is not relevant to the facts of the present application.

The Office further cites *Vas-Cath* for the proposition that the "...applicant must convey, with reasonable clarity to those skilled in the art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed." Applicants respectfully submit that the possession of the invention as claimed is conveyed with reasonable clarity, in that genes encoding the mRNA

sequences of the present invention, including the 5' UTRs from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase, have long been studied. The cloning and characterization of these genes were known in the art as of the effective filing date of the present claims. Further, as stated above, the instant claims now recite a specific folded state free energy, which further defines the relevant structural or physical characteristics of the claimed sequence. Combined with the working examples, these factors more than adequately convey possession of the claimed invention, satisfying the standard set forth in *Vas-Cath*.

Applicants may show evidence of possession of the entire genus by the relevant identifying characteristics of the group. These characteristics can be a complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, methods of making, or combinations of the above. *University of California; MPEP 2163*). The identifying characteristics in the present case are shown by the functional characteristics of the sequences. That is, the specific DNA sequences that are claimed in the present invention are those that, when transcribed, produce a messenger RNA sequence that comprises (a) a translatable sequence encoding a toxin, and (b) an untranslated sequence; wherein the untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells. Representative specific 5' UTRs and the specific identifying characteristics of a certain folded state free energy of $\Delta G \leq$ about -50 Kcal/Mol are also disclosed. Applicants respectfully submit that one skilled in the art would find the specific functional characteristics of the claimed sequences an adequate representation of the genus.

Given the concededly high level of skill in the art, it would be a routine matter to one skilled in the art to isolate untranslated mRNA sequences which inhibit translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress

eukaryotic initiation factor eIF4E and which allow translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells using the techniques disclosed in previous papers. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. See, *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) and *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

In view of at least the above arguments and amendments to the claims, applicants respectfully assert that the rejection under 35 USC § 112, First Paragraph, with respect to the Written Description requirement, have been overcome and should be withdrawn.

b. Enablement

The Office further rejected Claims 1-56 under 35 U.S.C. §112, First Paragraph, as not reasonably providing enablement for the full scope encompassed by the claims; specifically the Office has rejected the claims as not enabled for any route of administration other than administration directly to the target cells.

Applicants respectfully disagree. The specification meets the enablement requirements of §112 for the full scope of the claims in that the application discloses the intended patients, therapeutically effective amounts of the vector to be administered, exemplary routes of administration, the intended therapeutic product, and the intended disease. The specification does not broadly claim gene therapy techniques without demonstrated, working examples. In fact, the specification provides multiple working examples showing striking results. These examples show that the claimed DNA sequence were successfully delivered and expressed in both the in vitro and in vivo environment, resulting in a dramatic improvement in disease state.

As such, applicants respectfully submit that, in view of the extensive direction and guidance provided, the presence of working examples for in vitro and in vivo gene therapy, the relative breadth of the claims, and the evolved state of the art with respect to gene therapy at the

time of filing, practice of the claimed invention would not require undue experimentation, and the requirements of § 112, First Paragraph have been met.

The Office's concerns with respect to the application of the Wands factors are addressed in turn as follows:

The nature of the invention. Applicants submit that the nature of the invention lends itself to the fact that the amount of experimentation required to perform the broadly claimed methods is not undue. This factor supports the Applicants' contention that the disclosure does not require undue experimentation since methods of gene therapy known as gene directed enzyme prodrug therapy (GDEPT) were well-known in the art at the time of filing and the present invention utilizes a similar system. Koromilas AE (1992) *EMBO J.* **11**: 4153-4158; Johannes G (1999) *PNAS* **96**:13118-13123; McCormick F. (2001) *Nature Rev Cancer.* 1(2):130-41. Miller AD (1992). *Nature.* **357**: 455-460.

The breadth of the claims. Although the Office contends that the breadth of the claims is very broad in that the UTR can be any sequence having a relatively long palindromic oligonucleotide sequence that is self-complementary, the claim is not overly broad because Applicants have disclosed the concise mechanism of action that the claims of the present application require -- *i.e.,* that it requires an untranslated sequence that when placed in front of the open reading frame of the toxin gene, the untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells -- and that mechanism defines the breadth of the materials that work.

Additionally, claims 1, 13, 25 and 41 now recite the feature of an untranslated sequence further comprising a hairpin secondary structure conformation having a stability measured as folded state free energy of ΔG <about -50 Kcal/Mol. Therefore, the claims are not as broad as indicated by the Office. The scope of the present invention and embodiments falling within the claims are readily determined by those skilled in the art by commonly known procedures.

The unpredictability of the art and the state of the prior art. The Office appears to have taken the stance that gene therapy as a whole is unpredictable as a mode of delivery in order to provide sufficient expression of genes sufficient to provide curative effects. The Office goes on to cite references regarding the efficacy of GDEPT therapy. The Office indicates that the main technical hurdle related to gene therapy is efficient targeting and delivery to specific cells or tissues. What is not appreciated is that the present invention *eliminates this known problem of gene therapy* by eliminating the necessity of the vector to target specific cells. In the present invention, the genes may target any cell within the subject but will show a therapeutic effect only in tumor cells due to the specificity of the presence of eIF4E.

The Office further indicated that efficiency of transfer is an issue in gene therapy bearing on enablement, citing the discussion of Kirn, et al. Applicants respectfully disagree that this factor renders the claimed invention not enabled. Efficiency, particularly in the context of the instant invention, need not be 100%, or even close to 100%, to enable one of skill in the art to practice the invention. As explained in DeFatta, et al, Gene Cancer Therapy 2002, it has been shown that, using the HTK/GCV system, when as few as 10% of the cancer cells express HTK, it is possible to obtain complete tumor ablation due to the bystander effect and specific immune responses. As such, low efficiency of transfer is not a measure of enablement with respect to the instant invention.

Applicants respectfully traverse this rejection in light of the showing of working examples in the specification, the predictability of the art for the claim scope, the correlation of working examples of the claimed invention, the correlation of working examples in the prior art to the claimed invention, and the correlation of animal models to the disease. Applicants have provided sufficient detailed examples in the specification showing tumor ablation in mice injected with the present vectors. The U.S. Patent Office clearly does not require clinical data for gene therapy claims and that while gene therapy taken as a whole may be unpredictable, particular embodiments are patentable. Applicants have provided sufficient detail of particular patentable embodiments.

The unpredictability of the art and the state of the prior art. At the time of filing, gene therapy techniques, particularly those using the HTK sequence, were known and practiced in the art. In fact, applicants have referenced successful applicant of gene therapy techniques in their disclosure, specifically at paragraph [0005].

Working Examples and Guidance in the Specification. The Office contends that the examples are insufficient for enablement, stating that tumor-specific expression of the toxin using GDEPT systems was critical for effective therapeutic treatment. This reasoning does not apply, however, in that the essence of the instant invention is that tumor-specific promotors are not necessary due to the discovery that elevated levels of eIF4E, as found in tumor cells, permit selective translation of the toxin when 5' untranslated sequences having the claimed properties are used. As such, a tumor-specific promoter is not necessary, and the instant invention overcomes the shortcomings of the prior art.

The Office further contends that the examples are insufficient to enable application of the methods to immunocompetent subjects. The Office argues that the working examples only show systemic administration of a DNA to an immunocompromised mouse, having no working examples showing systemic administration of a DNA to a mouse having a fully functional immune system. The Office further argues lack of enablement on the basis that there are no working examples showing systemic administration of an mRNA to any subject as encompassed by some of the claims. With respect to this rejection, applicants respectfully assert that 1) the immunocompromised mouse is known to be a sufficient model for demonstrating effective gene therapy techniques that could be extrapolated to immunocompetent subjects; 2) the scientific community has long accepted the use of immunodeficient (athymic nude or SCID) mice to study HSV-TK suicide gene therapy; 3) the FDA has long recognized the use of immunocompromised mice for extrapolation of preclinical data for IND submissions for HSV-TK gene therapy approaches in individuals with fully functioning immune systems; 4) the inventors have demonstrated efficacy in immunocompetent (BalbC mice) in addition to the immunocompromised mice (see DeFatta RJ, Chervenak RP, De Benedetti A. A cancer gene therapy approach through translational control of a suicide gene. Cancer Gene Ther. 2002

Jun;9(6):505-12.; and 5) immune status does not appear to play a role in determining efficacy of translational control for HSV-TK gene therapy (See, for example, Chu QD, Sun L, Li J, Byrnes K, Chervenak D, Debenedetti A, Mathis JM, Li BD. Rat adenocarcinoma cell line infected with an adenovirus carrying a novel herpes-simplex virus-thymidine kinase suicide gene construct dies by apoptosis upon treatment with ganciclovir. J Surg Res. 2007 Nov;143(1):189-94; Byrnes K, Li BD, Holm N, Li J, Okadata Y, De Benedetti A, Nedeljkovic-Kurepa A, Mathis M, Chu QD. A novel suicide gene therapy targeting the overexpression of eukaryotic initiation factor 4E improves survival in a rat peritoneal carcinomatosis model. Surgery. 2007 Aug;142(2):270-5.). Applicants further respectfully assert that the Office has not provided convincing evidence as to why the results achieved using the art-recognized model disclosed in applicants' specification cannot be correlated to efficacy in non-human primates or humans.

Quantity of Experimentation. The Office has conceded that the art recognizes that a high level of experimentation is required for the development of a viable and efficacious GDEPT cancer therapy, citing Kirn et al. The Office has expressed concern, however, that determining the reliability and efficacy of the proposed GDEPT system is very large, and therefore undue. Applicants respectfully disagree for at least the following reasons.

Applicants respectfully disagree. As set forth above, applicants have provided working examples that show the use of different DNA sequences to control gene expression that constitutively expresses the toxin in all cell types. The determination of the appropriate vector and dosage of plasmid DNA or levels of expression that would be effective in treating tumors and the proper sequence for expressing the toxin in the tumor cells would necessarily be determined empirically and would be merely routine. Dosages of therapeutic agent effective in treating tumors are routinely extrapolated by methods known in the art.

An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. "The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed." *In re Wands*, 8 USPQ2d at 1404 (CCPA 1076). The time and expense are merely factors in this consideration and are not the controlling factors.

The sequences that fall within the scope of the present claims are easily ascertained by any person skilled in the present art. The scope of the claims requires that the sequence is capable of being transcribed to produce a messenger RNA sequence that comprises a translatable sequence encoding a toxin and furthermore comprising an untranslated sequence wherein the untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells, and wherein the untranslated sequence has a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G \leq$about -50 Kcal/Mol

It is well within the scope of ability of one skilled in the art to test sequences of the present invention for the following reasons: (1) the amount of testing required is relatively small especially since most of the work can be done with tissue culture experiments as the proof of principle with the animal studies was already provided; (2) testing of any particular sequence in question would not require direction or guidance beyond that known in the art; (3) the current state of knowledge in the art and relative skill of those in the art is quite high; (4) well-known procedures exist for sequencing various DNA sequences capable of producing a messenger RNA sequences that comprises an untranslated palindromic sequences; and (5) determining whether or not a sequence falls within the scope of the claims is quite straightforward since all of the materials and methods that would be required to determine if a particular untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

Level of the skill in the art. The Office concedes that the level of the skill in the art is deemed to be high. As such, applicants assert that, given the extensive disclosure, including working examples, provided by applicant and the high skill in the art, successful practice of the invention is not undue. In fact, in view of the working examples described by applicants, successful application of the claimed methods is well within reach of one of ordinary skill in the art.

In view of the amendments to the claims and Applicant's arguments set forth above, applicants respectfully submit that the claims as pending do not require undue experimentation, and sufficiently meet the standard for enablement. As such, applicants respectfully request reconsideration and allowance of the claims.

Claim Rejections - 35 USC § 102

The Office has rejected claims 1-25, and 41-56 under 35 U.S.C. §102(a) as being anticipated by DeFatta. (Dissertation cataloged and shelved on March 20, 2001). Applicants herewith submit a Declaration under 37 CFR §1.132 traversing the rejection by showing that the inventorship of the present application is correct and that the reference discloses subject matter derived from the Applicants rather than invented solely by the author of the published article notwithstanding the authorship of the article, *i.e.*, that Applicants are the inventors of the subject matter disclosed in the article and claimed in the application. Accordingly, this rejection has been overcome and should be withdrawn.

Conclusion

Based on the foregoing amendments and remarks, as well as the attached Declarations under 37 CFR 1.132, it is submitted that the present application is now in form for allowance. Therefore, early reconsideration and allowance of the claims, as currently pending, are solicited.

The Assistant Commissioner for Patents is authorized to charge any deficiency or credit any overpayment to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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*by*_____

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